Functional impacts of NRXN1 knockdown on neurodevelopment in stem cell models.

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Public Summary:
This work use human IPS cell to study the mechanisms of autisms.

Scientific Abstract:
Exonic deletions in NRXN1 have been associated with several neurodevelopmental disorders, including autism, schizophrenia and developmental delay. However, the molecular mechanism by which NRXN1 deletions impact neurodevelopment remains unclear. Here we used human induced pluripotent stem cells (hiPSCs) and human embryonic stem cells (hESCs) as models to investigate the functional impacts of NRXN1 knockdown. We first generated hiPSCs from skin fibroblasts and differentiated them into neural stem cells (NSCs). We reduced NRXN1 expression in NSCs via a controlled shRNAmir-based knockdown system during differentiation, and monitored the transcriptome alteration by RNA-Seq and quantitative PCR at several time points. Interestingly, half reduction of NRXN1 expression resulted in changes of expression levels for the cell adhesion pathway (20 genes, P = 2.8x10(-6)) and neuron differentiation pathway (13 genes, P = 2.1x10(-4)), implicating that single-gene perturbation can impact biological networks important for neurodevelopment. Furthermore, astrocyte marker GFAP was significantly reduced in a time dependent manner that correlated with NRXN1 reduction. This observation was reproduced in both hiPSCs and hESCs. In summary, based on in vitro models, NRXN1 deletions impact several biological processes during neurodevelopment, including synaptic adhesion and neuron differentiation. Our study highlights the utility of stem cell models in understanding the functional roles of copy number variations (CNVs) in conferring susceptibility to neurodevelopmental diseases.